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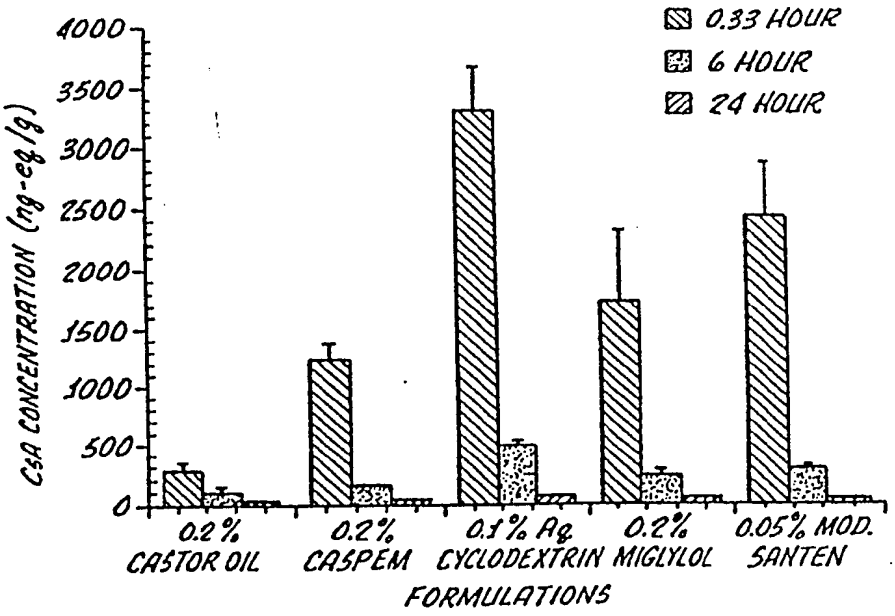

(57) Abstract

A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one cyclosporin in admixture with a higher fatty acid glyceride and polysorbate 80. More particularly, the cyclosporin may be cyclosporing A and the higher fatty acid glyceride may be castor oil. Composition has been found to be of a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues with enhanced absorption in the lacrimal gland. In addition, the composition has stability for up to nine months without crystallization of cyclosporin.

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LACRIMAL GLAND SPECIFIC EMULSIONS FOR TOPICAL APPLICATION TO OCULAR TISSUE

This application is a continuation-in-part of pending US patent application SN 08/243,279 filed May 17, 1994.

The present invention generally relates to novel pharmaceutical compositions incorporating chemicals which are poorly soluble in water and is more particularly related to a novel ophthalmic emulsion including cyclosporin in admixture with castor oil and polysorbate 80 with high comfort level and low irritation potential.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. In addition, as set forth in U.S. Patent No. 4,839,342, cyclosporin (sometimes referred to in the literature as "cyclosporine") has been found as effective in treating immune medicated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.

As hereinabove noted, cyclosporin comprises a group of cyclic oligopeptides and the major component thereof is cyclosporin A ($C_{62}H_{111}N_{11}O_{12}$)which has been identified along with several other minor metabolites, cyclosporin B through I. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different

substituents or configurations of some of the amino acids.

It should be appreciated that reference to the term "cyclosporin" or "cyclosporins" is used throughout the present specification in order to designate the cyclosporin component in the composition of the present invention.

However, this specific reference is intended to include any individual member of the cyclosporin group as well as admixtures of two or more individual cyclosporins, whether natural or synthetic.

The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.

This activity can be enhanced if it is possible to enhance the absorption of the cyclosporin in the lacrimal gland. The present invention provides for a formulation and method that produces optimal cyclosporin A concentrations in the lacrimal gland and other ocular surface tissues.

Unfortunately, the solubility of cyclosporin in water is extremely low and as elaborated in U.S. Patent No. 5,051,402, it has been considered not merely difficult but practically impossible to prepare a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium.

As reported, the solubility of cyclosporin in water is between about 20 μg/ml to 30 μg/ml for cyclosporin A. Hence, heretofore prepared formulations incorporating cyclosporin have been prepared as oily solutions containing ethanol. However, these

preparations limit the bioavailability to oral preparations and this is believed to be due to the separation of cyclosporin as a solid immediately after it comes into contact with water, such as in the mouth or eye of a patient.

In the case of injectable preparations of cyclosporin, they first must be diluted with physiological saline before intravenous administration but this is likely to result in the precipitation of cyclosporin and therefore may be considered undesirable for intravenous administration.

Surface active agents such as polyoxyethylated castor oil have been utilized as solubilizers to inject preparations in order to prevent cyclosporin from separating. However, this also may give rise to safety problems (see U.S. Patent No. 5,051,402).

The practical usefulness of cyclosporin would be greatly enhanced if administration thereof could be effective; for example, cyclosporin's effectiveness in the treatment of ocular symptoms of Behcet's Syndrome. However, if it is administered orally for the treatment of these symptoms, the accompanying side effects due to systemic circulation may cause adverse reactions such as hypertrichosis or renal dysfunction.

On the other hand, if oily preparations containing cyclosporin are applied directly to the eyes, irritation or a clouding of visual field may result. This plus the difficulty in formulating cyclosporin limits its use in formulations that would be useful during keratoplasty as well in the treatment of herpetic keratitis and spring catarrh.

Heretofore, as for example in U.S. Patent No. 5,051,402, attempts have been made to dissolve sufficient cyclosporin in an aqueous solvent system so as to reach an effective concentration for treatment. Importantly, this solvent system does not contain any surface active agent such as polyoxyethylated castor oil.

Conceptually, the purpose of dissolving the cyclosporin in an aqueous solvent system is to enable contact with body fluids which would merely constitute dilution of the aqueous solvent system which hopefully would eliminate the immediate precipitation of cyclosporin when contacted with the water content of the body fluids.

For direct use in the eye, cyclosporin has been formulated with a number of pharmaceutically acceptable excipients, for example, animal oil, vegetable oil, an appropriate organic or aqueous solvent, an artificial tear solution, a natural or synthetic polymer or an appropriate membrane.

Specific examples of these pharmaceutically acceptable excipients, which may be used solely or in combination, are olive oil, arachis oil, castor oil, mineral oil, petroleum jelly, dimethyl sulfoxide, chremophor, liposomes, or liposome-like products or a silicone fluid, among others.

In summary, a great deal of effort has been expended in order to prepare a pharmaceutical composition containing cyclosporin dissolved in an aqueous medium or cyclosporin prepared as an oily solution. However, successful formulations have yet to be accomplished as evidenced by the lack of commercial products.

As hereinabove noted, it has been reported that cyclosporin has demonstrated some solubility in oily preparations containing higher fatty acid glycerides such as olive oil, peanut oil, and/or castor oil. These formulations frequently produce an unpleasant sensation when applied to the eye because of stimulation or the viscousness which is characteristic of these oils.

Another drawback of these formulations is that they contain a high concentration of oils, and oils exacerbate the symptoms of certain ocular surface diseases such as dry eyes, indicated by cyclosporin. Therefore, these oily formulations may not be clinically acceptable. Additionally, these formulations often suffer from physical instability due to cyclosporin's propensity to undergo conformational change and crystallize out. The crystallization problem has been noticed in formulations containing corn oil or medium chain triglycerides. Lastly, these formulations often have a low thermodynamic activity (degree of saturation) of cyclosporin which leads to a poorer drug bioavailability.

It may be possible to minimize the problems related to unpleasant sensation and syndrome exacerbation by reducing the oil content and dispersing the oil phase in water into an emulsion. However, it is not an easy task to formulate an ophthalmic emulsion because one indispensable class of ingredients in an emulsion system is emulsifiers, and the majority of emulsifiers is highly irritating to the eyes.

The present invention is directed to an emulsion system which utilizes higher fatty acid glycerides but in combination with polysorbate 80 which results in an emulsion with a high comfort level and low irritation

potential suitable for delivery of medications to sensitive areas such as ocular tissues. Further, the present invention provides a pharmaceutical composition and method for causing preferential absorption of cyclosporin in the lacrimal gland. That is, for a given instillation of the composition into an eye, a greater amount of absorption occurs in the lacrimal gland for formulations made in accordance with the present invention than heretofore utilized formulations.

SUMMARY OF THE INVENTION

In accordance with the present invention, a non-irritating pharmaceutical composition with high comfort level and low irritation potential suitable for delivery to sensitive areas such as ocular tissues comprises cyclosporin in admixture with an emulsifying amount of a higher fatty acid glycerol and polysorbate 80. More particularly, the composition may comprise cyclosporin A and the higher fatty acid glyceride may comprise castor oil.

Preferably, the weight ratio of the castor oil to the polysorbate 80 is between about 0.3 to about 30 and a weight ratio of the cyclosporin to castor oil is below 0.16. More preferably, the weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5, and the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02.

When cyclosporin is dissolved in the oil phase in accordance with the present invention, the emulsion is found to be physically stable upon long term storage. No crystallization of cyclosporin was noticed after nine months at room temperature. Moreover, the cyclosporin emulsion is formulated in such a way that

the drug has reasonably high thermodynamic activity, yet without the crystallization problem.

Importantly, the composition of the present invention provides for enhanced absorption of the cyclosporin in the lacrimal gland of the eye. In this manner, the activity of the cyclosporin in restoring lacrimal gland tearing is increased. That is, since a greater amount of cyclosporin is absorbed into the lacrimal gland, more of the cyclosporin is effective in producing lacrimal gland tearing than heretofore possible.

BRIEF DESCRIPTION OF THE DRAWINGS

The advantages and features of the present invention will be better understood by the following description when considered in conjunction with the accompanying drawings in which:

Figure 1 is a bar chart of conjunctival concentration of cyclosporin A after a single topical instillation of various formulations in a rabbit eye;

Figure 2 is a bar chart of cornea concentration of cyclosporin A after a single topical instillation of various formulations in a rabbit eye;

Figure 3 is a bar chart of ciliary body concentration of cyclosporin A after a single topical instillation of various formulations in a rabbit eye; and

Figure 4 is a bar chart of lacrimal gland concentration of cyclosporin A after a single topical instillation of various formulations in a rabbit eye.

DETAILED DESCRIPTION

As hereinabove noted, cyclosporin is available as a mixture in which the principal ingredient is cyclo-

sporin A with significant, but smaller, quantities of other cyclosporins such as cyclosporin B through I. However, as also hereinabove noted, the present invention may be applied to either a pure cyclosporin or to a mixture of individual cyclosporins.

The discovery on which the present invention is founded relates to a combination of a higher fatty acid glyceride and an emulsifier and dispersing agent, polysorbate 80. The selection of these components could not have been anticipated on the basis of conventional thinking.

For example, although it is well known that cyclosporin may be used in combination with castor oil, this combination is irritating to sensitive tissues such as the eye. Thus, conventional teaching in the art is away from a formulation which utilizes a higher fatty acid glyceride, such as castor oil, and cyclosporin.

Stated another way, there is no way of deducing that the use of an emulsifier and dispersing agent such as polysorbate 80 will reduce the irritation potential of an emulsion utilizing castor oil. There are no examples of polysorbate in combination with castor oil which, when admixed to cyclosporin, produces an emulsion with a high comfort level and low irritation potential suitable for the delivery of medication to sensitive areas such as ocular tissues.

The present invention achieves a <u>stable solution state</u> of cyclosporin. This stable solution state is another important performance characteristic differentiating the present invention from the conventional oil systems. Cyclosporin is notorious for its ten-

dency to precipitate out in conventional oil systems in which it is fully dissolved initially.

In accordance with the present invention, the emulsions can be further stabilized using a polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen®.

Pemulen® is a polymeric emulsifier having a CTFA name of Acrylates/C10-30 Alkyl Acrylate Cross-Polymer and is discrived in th "Carbomer 1342" monograph in the USPXXII/NFXVII.

In addition, the tonicity of the emulsions can be further adjusted using glycerine, mannitol, or sorbitol if desired. The Ph of the emulsions can be adjusted in a conventional manner using sodium hydroxide to a near physiological pH level and while buffering agents are not required, suitable buffers may include phosphates, citrates, acetates and borates.

While the preferable medications in accordance with the present invention include cyclosporin, other chemicals which are poorly soluble in water such as indomethacin and steroids such as androgens, prednisolone, prednisolone acetate, fluorometholone, and dexamethasones, may be emulsified with castor oil and polysorbate 80 resulting in a composition with similar low irritation potential.

The invention is further illustrated by the following examples with all parts and percentages expressed by weight. The cyclosporin used in the examples was supplied by Sandoz.

Example 1

	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6

Example 2

	A	B	C	D
Castor oil	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%
Pemulen®	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs
Purified water	qs	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6

Example 3

	A
Castor oil	2.50%
Polysorbate 80	0.75%
Carbomer 1382	0.05%
Glycerine	2.20%
NaOH	qs
Purified water	qs
pH	7.2-7.6

Example 4

	A
Castor oil	5.00%
Polysorbate 80	0.75%
Carbomer 981	0.05%
Glycerine	2.20%
NaOH	qs
Purified water	qs
pH	7.2-7.6

The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome with Examples 2, 3 and 4 without the active ingredient cyclosporin utilized to determine the toxicity of the emulsified components.

The formulations in Examples 1-4 were applied to rabbit eyes eight times a day for seven days and were found to cause only slight to mild discomfort and slight hyperemia in the rabbit eyes. Slit lamp examination revealed no changes in the surface tissue. In addition, the cyclosporin containing castor oil emulsion, as hereinabove set forth in Examples 1A-1D, was also tested for ocular bioavailability in rabbits; and the therapeutic level of cyclosporin was found in the tissues of interest after dosage. This substantiates that cyclosporin in an ophthalmic delivery system is useful for treating dry eye as set forth in U.S. Patent No. 4,839,342.

In addition, no difference in toxicity was found between formulations with cyclosporin (Examples 1A-1D) and formulations without cyclosporin (Examples 2-4).

The formulations set forth in Examples 1-4 were found to be physically stable upon long term storage.

With regard to formulations 1A-1D, no crystallization of cyclosporin was noticed after nine months at room temperature.

Further, other higher fatty acid glycerides such as olive oil, peanut oil and the like may also be utilized with the polysorbate 80 with similar results regarding biotoxicity.

The following examples demonstrate the activity of the composition in accordance with the present invention for enhanced absorption of cyclosporin A in the lacrimal gland.

Materials

The [Mebmt-^{3}H]-cyclosporin-A (lot #TRQ6553) was prepared by Amersham International (Buckinghamshire, England) with radiochemical purity of -98% (by reversed phase HPLC) and specific activity of 2.6 Ci/mmol (2.16 mCi/mg). The ^{3}H-label is a metabolically stable position as shown by the asterisk. The radiolabeled CsA was supplied as an ethanol solution (1 mCi/ml). All organic solvents used in the procedures described in this study were "HPLC grade". all other chemicals and reagents were analytical grade unless otherwise noted.

The compositions of the six formulations tested are listed in Table A.

TABLE A

Ingredients	Castor Oil	Castor Oil-in-Water Emulsion	Aqueous-α Cyclo-dextrin	Miglyol Oil-in-Water Emulsion	Polyoxyl 40	Polyoxyl 40 with Edetate
Cyclosporin-A	0.20	0.20	0.10	0.20	0.05	0.05
Cyclodextrin			14			
Castor Oil	99.8	1.25				
Miglyol Oil				20		
Pluronic L121+P123				0.75		
Tween 80		1.00				
Glycerin		2.20		2.20		
Pemulen® TR-2		0.05				
Carbopol 981				0.05		
Polyoxyl 40 Stearate (mg)					20	20
HPMC					0.3	0.3
Butylated Hydroxytoluene					0.001	0.001
Ethanol(9200 proof)						0.1
Sodium Chloride					0.73	0.73
Sodium Monophosphate					0.2	0.2
Disodium Edetate						0.1
Water		QS	QS	QS	QS	QS
Batch Size	1 g	5 g	1 g	5 g	1 g	1 g

The radiolabeled formulations were formulated to ensure that the radioactivity was homogeneous throughout the vehicle. The expected radioactivity concentrations of the radiolabeled drug formulations were 1-2 mCi/ml. The expected specific activity of radiolabeled cyclosporin A (CsA) formulations was 0.5-2 mCi/mg. All test articles were stored at ambient temperature.

Analysis of Test Drug Formulations

The test formulations were analyzed in triplicate by HPLC to determine the concentration of CsA and radiochemical purity of the CsA dosing solutions (>93%) before dosing. The radioactive concentrations of the test formulations were quantified by liquid scintillation counting (LSC).

Chromatographic Conditions

Pump:	Beckman Model 126 (Beckman Instruments, San Ramon, CA)
Mobile phase:	Acetonitrile: 0.03% H_3PO_4 in water, pH 3 (65:35 v/v)
Flow rate:	1.0 ml/min
Column:	Supercosil C8, 7.5 cm x 4.6 mm, 3 μm (Supelco, Bellefonte, PA) Superguard LC-8 (Supelco) Column heater (Bio-rad, Richmond, CA) at 60-70°C
Injector:	WISP 712B (Waters Associates, Milford, MA)
^{14}C detector:	Radio Isotope 171 Detector (Beckman Instruments)
Scintillant:	Ready Flow III (Beckman Instruments), Flow Rate of ~4 ml/min
UV detector:	Model 166 (Beckman Instruments), 202 nm
Data processor:	Beckman System Gold (Beckman Instruments)
Run Time:	15 min
Retention Time:	6 min (cyclosporin A)

Animals

Female New Female New Zealand albino rabbits were obtained and quarantined for at least five days before procedures. Animals were housed in temperature- and humidity-controlled rooms. Food and tap water were provided *ad libitum*. Fifty-eight rabbits (2-3 kg) were selected from the colony to minimize bias. They were individually identified by ear tags and appeared to be healthy.

Dosing

The animals were divided into six groups of nine rabbits; each group was treated with one of the six CsA formulations. During dosing, the lower eyelid of each rabbit was gently pulled away from the eye and 35 µl of the formulation were administered in the lower conjunctival cul-de-sac of each eye. After dosing, the upper and lower eyelid were handheld closed for ~5 seconds and released. The animals were observed visually for any signs of tearing or ocular discomfort.

Sampling

Tissues were collected at 20-min., 6-hr. and 24-hr. post-dose for each group. Three rabbits (six eyes) were used at each time point. At the specific sampling times, the animals were euthanized by an intravenous injection of 0.5-1 ml Eutha-6 (Western Supply Co., Arcadia, California) via marginal ear vein. Each eye was then rinsed with normal saline. The aqueous humor (~200 µl) was removed by means of a 0.5 ml tuberculin syringe. The orbital lacrimal gland (~400 mg), upper and lower bulbar conjunctivae (~50 mg each), corneal (~50 mg) and iris-ciliary body (~50 mg)

were dissected. The tissues dissected were blotted dry and weighed. Ocular tissue and aqueous humor samples from both eyes were collected from four untreated animals to be used as blank samples.

Analysis of Radioactivity

An aliquot of aqueous humor (50-175 μl) was counted directly in 10 ml of Ready-Solv HP by LSC. Tissue and blood samples were weighed into combustion cones prior to combustion in a Model 307 Packard Tissue Oxuduzer (Packard Co., Downers Grove, Illinois). After combustion of the tissue samples, ^3H_2O was trapped in the Monophase-S solution (Packard) and the radioactivity of the samples was determined by LSC in a Beckman Model 1801 or 3801 scintillation counter (Beckman Instruments, San Ramon, California).

Data Analyses

Excel software (version 4.0, Microsoft Corp, Redmond, Washington) was used for data analysis. concentrations of total radioactivity in the tissue samples were expressed as dpm/g or dpm/ml and converted to ng equivalents (eq) of CsA/g or ml, using the specific activity of the dosing formulations. Mean, standard deviation (SD) or standard error of the mean (SEM) was calculated according to standard methods. Radioactivity levels were not considered significant unless the dpm was greater than twice that of background b=(blanks).

Comparisons of tissue drug concentrations at each time point for the formulations were determined by one-factor ANOVA. All statistical comparisons were made using StatView® (version 1.03, Abacus Concepts, Inc., Berkeley, California). the Fisher and Scheffe

F tests were used to determine significant differences between formulations at the 95% level ($\alpha = 0.05$). The rejection criteria for excluding any outlier data was based on standard outlier tests. No more than one outlier was eliminated from any data set.

Results and Discussion

The radioactivity concentrations in ocular tissues at 20 minutes, 6 hours, and 24 hours after a single topical application of various formulations are depicted in Figures 1-4. In general, the concentrations in the ocular tissues were greatest at the earliest time point of 20 minutes as reported in previous single dose studies (2, 3). The radioactivity concentration was highest in the conjunctiva and cornea for each formulation. The relatively low aqueous humor and iris-ciliary body concentrations suggest low intraocular absorption of CsA, consistent with the low CsA corneal permeability of $\sim 1.0 \times 10^{-6}$ cm/sec (6). The decline of radioactivity concentrations from the cornea was slower than those from the conjunctiva, lacrimal gland, and aqueous humor. The observed blood radioactivity concentrations (<3 ng-eq/ml) were much lower than trough plasma CsA concentrations of 80-250 ng/ml observed after oral dosing to humans (1).

The dependence of CsA corneal and conjunctival penetration on the formulation was interpreted in terms of CsA concentration in formulation and the release rate of CsA from formulation into tear film. The aqueous formulations demonstrated a greater propensity to release CsA for diffusion across the surface tissue epithelia. The 0.2% straight castor oil was formulated below the CsA solubility and therefore the release rate could be hampered by the less than maximal CsA thermodynamic activity (5).

The ocular surface tissues contained a higher fraction of the CsA dose than the other tissues and was used to discriminate among the aqueous, emulsion and the straight castor oil formulations. The polyoxyl 40 formulation produced higher ocular surface tissue concentrations than the emulsions and straight castor oil. The emulsions were also effective in delivery of CsA to the tissues of interest, lacrimal gland, cornea, and conjunctiva. The castor oil emulsion showed higher lacrimal gland concentrations than the modified Santen and the miglyol emulsion. The straight castor oil showed the lowest concentrations in surface ocular tissues. Apparently, the factors influencing CsA penetration into the lacrimal gland and the surface tissues are different.

Although there has been hereinabove described a particular pharmaceutical composition in the form of a nonirritating emulsion for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto. Accordingly, any and all modifications, variations, or equivalent arrangements, which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A composition comprising a nonirritating emulsion of at least one cyclosporin in admixture with a higher fatty acid glyceride, polysorbate 80 and an emulsion-stabilizing amount of Pemulen® in water suitable for topical application to ocular tissue.

2. The pharmaceutical composition according to claim 1 wherein the cyclosporin comprises cyclosporin A.

3. The pharmaceutical composition according to claim 2 wherein the weight ratio of the higher fatty acid glyceride to the polysorbate 80 is between about 0.3 and about 30.

4. The pharmaceutical composition according to claim 3 wherein the higher fatty acid glyceride comprises castor oil and the weight ratio of cyclosporin to castor oil is below about 0.16.

5. A pharmaceutical composition comprising a nonirritating emulsion of at least one cyclosporin in admixture with castor oil and polysorbate 80 in water suitable for topical application to ocular tissue.

6. The pharmaceutical composition according to claim 5 wherein the cyclosporin comprises cyclosporin A.

7. The pharmaceutical composition according to claim 6 wherein the weight ratio of castor oil to the polysorbate 80 is between about 0.3 and about 30.

8. The pharmaceutical composition according to claim 7 wherein the weight ratio of cyclosporin to castor oil is below about 0.16.

9. The composition according to claim 1 wherein the higher fatty acid glyceride and polysorbate 80 are present in amounts sufficient to prevent crystallization of cyclosporin for a period of up to about nine months.

10. A stable, nonirritating ophthalmic composition comprising cyclosporin in admixture with an emulsifying amount of a higher fatty acid glyceride and polysorbate 80.

11. A pharmaceutical emulsion comprising cyclosporin A, castor oil, Pemulen®, glyceride and water in amounts sufficient to prevent crystallization of cyclosporin A for a period of up to about nine months, said pharmaceutical emulsion being suitable for topical application to ocular tissue.

12. The pharmaceutical emulsion according to claim 11 wherein the cyclosporin A is present in an amount of between about 0.05 to about 0.40%, by weight, the castor oil is present in ana mount of between about 0.625%, by weight, the polysorbate 80 is present in an amount of about 1.0%, by weight, the Pemulen® is present in an amount of about 0.05%, by weight, and the glyceride is present in an amount of about 2.2%, by weight.

13. A pharmaceutical emulsion consisting of between about 0.05% and about 0.40%, by weight, cyclosporin A, between about 0.625% and about 5.0%, by weight, castor oil, about 1.0%, by weight, polysorbate 80, about 0.05%, by weight, Pemulen®, and about 2.2%,

by weight, glycerine in water with a pH of between about 7.2 and 7.6 suitable for topical application to ocular tissue.

14. A pharmaceutical composition suitable for instillation into an eye, said pharmaceutical composition comprising a nonirritating emulsion of at least one cyclosporin and castor oil in an amount causing enhanced lacrimal gland absorption.

15. The pharmaceutical composition according to claim 14 wherein the cyclosporin comprises cyclosporin A.

16. The pharmaceutical composition according to claim 15 wherein the cyclosporin is present in an amount of between about 0.20 and about 5.0% by weight.

17. The pharmaceutical composition according to claim 15 further comprising an emulsion-stabilizing amount of Pemulen® in water suitable for topical application in the eye.

18. The pharmaceutical composition according to claim 17 wherein the cyclosporin is present in an amount of about 0.20% by weight, the castor oil is present in an amount of about 1.25% by weight, and the Pemulen® is present in an amount of about 0.05% by weight.

19. The pharmaceutical composition according to claim 18 further comprising Tween 80 in an amount of about 1.0% by weight, and glycerin in an amount of about 2.20% by weight.

20. A pharmaceutical composition suitable for instillation into an eye, said pharmaceutical

composition comprising a nonirritating admixture of at least one cyclosporin and castor oil in an amount causing enhanced lacrimal gland absorption.

21. The pharmaceutical composition according to claim 20 wherein the cyclosporin comprises cyclosporin A.

22. A method of causing enhanced absorption of cyclosporin A in the lacrimal gland of an eye, said method comprising the steps of:

admixing cyclosporin A with castor oil; and

instilling the admixture into the eye.

23. The method according to claim 22 wherein the step of admixing includes forming an emulsion of cyclosporin A, castor oil and water.

24. A method of causing enhanced absorption of cyclosporin A in the lacrimal gland of an eye, said method comprising the steps of:

forming an emulsion of cyclosporin A, castor oil, Pemulen® and water; and

instilling the emulsion into the eye.

25. The method according to claim 24 wherein the cyclosporin is present in an amount of about 0.20% by weight, the castor oil is present in an amount of about 1.25% by weight, and the Pemulen® is present in an amount of about 0.05% by weight.

26. The method according to claim 24 wherein the emulsion further comprises Tween 80 in an amount of about 1.0% by weight, and glycerin in an amount of about 2.20% by weight.

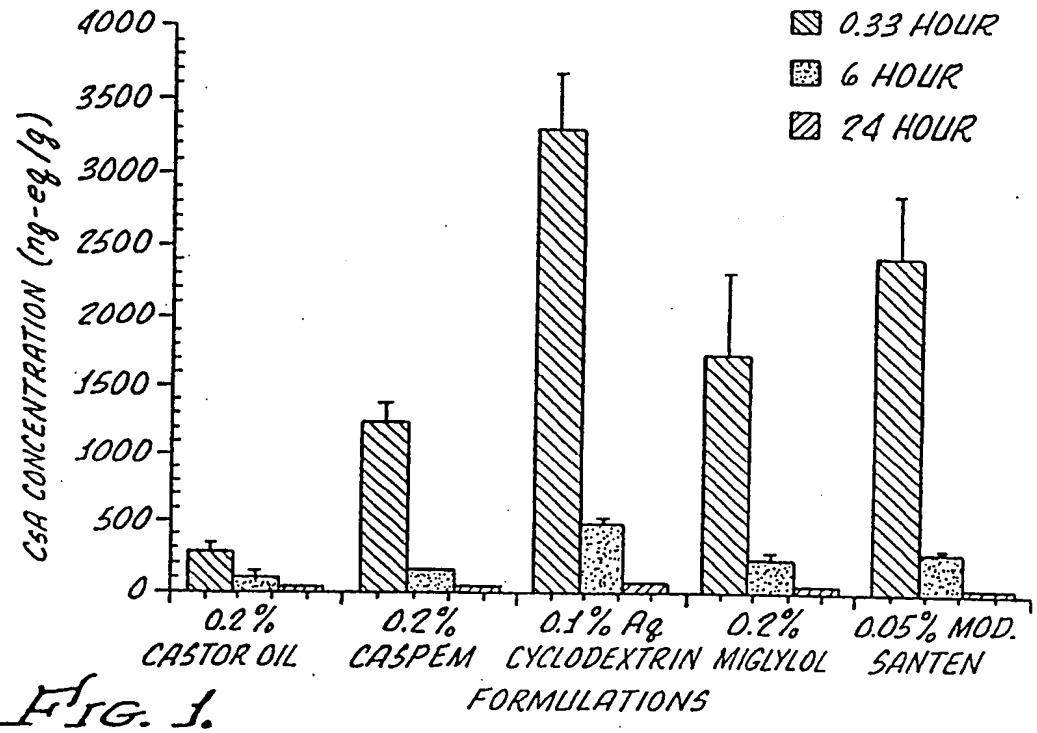


FIG. 1.

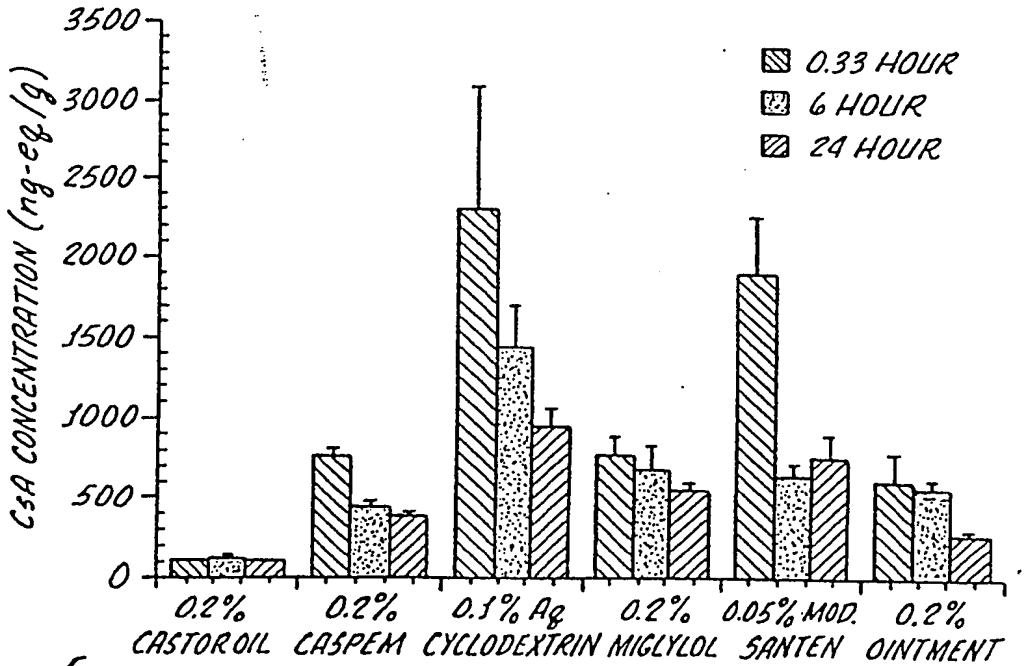
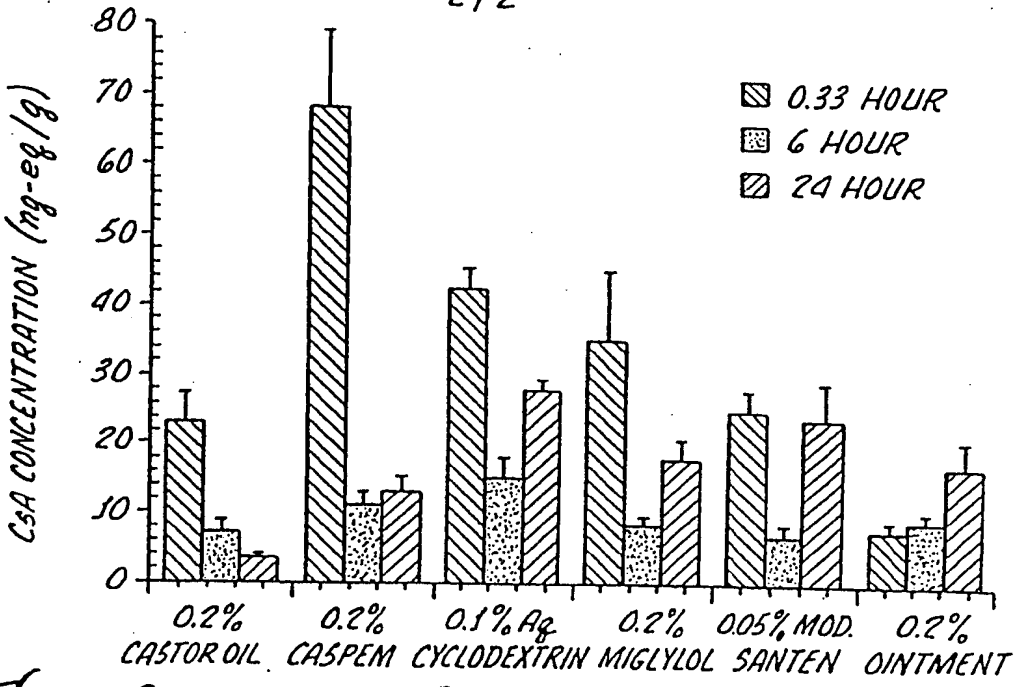


FIG. 2.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0.2% CASPEM
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0.2% MIGLYLOL
0.05% MOD. SANTEN
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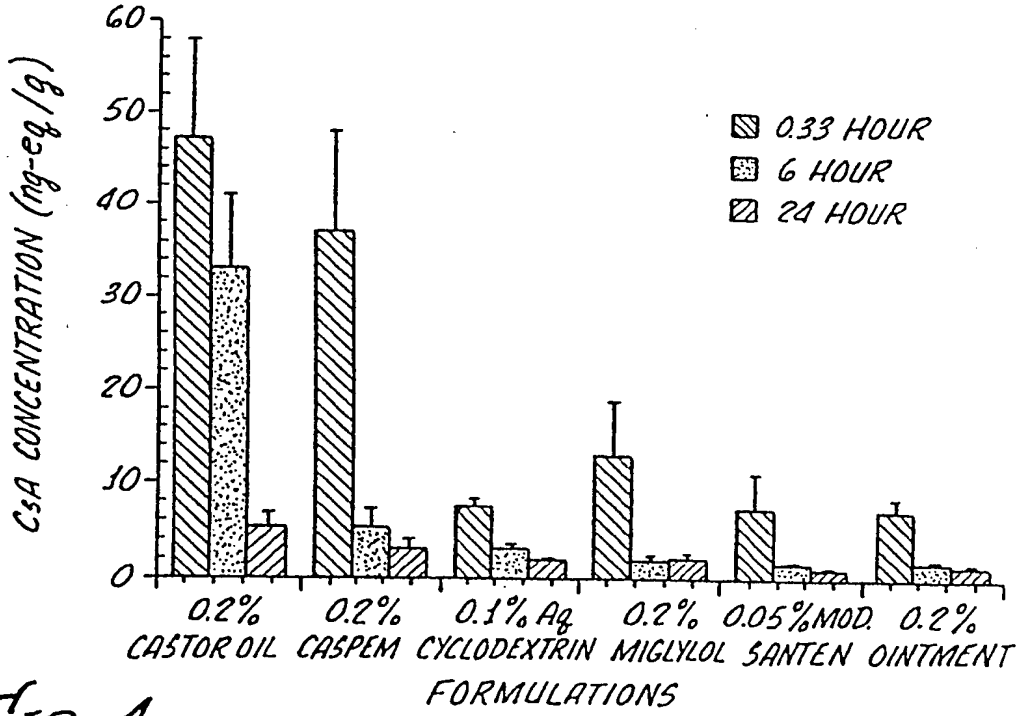
FORMULATIONS

FIG. 3.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FORMULATIONS

FIG. 4.

INTERNATIONAL SEARCH REPORT

Inten ıal Application No
PCT/US 95/06302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/13 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	GB,A,2 228 198 (SANDOZ LTD.) 22 August 1990 see claim 1 see page 13, paragraph 2 see page 27, paragraph 3	10 5-8
X Y	WO,A,89 01772 (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION INC.) 9 March 1989 see claims 11-13,15 see page 10, line 17 - line 31 see page 11, line 11 - line 17	14-16, 20,23 5-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 1995	26.09.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter .nal Application No
PCT/US 95/06302

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2228198	22-08-90	BE-A-	1005236	08-06-93
		CH-A-	680650	15-10-92
		DE-A-	4005190	23-08-90
		FR-A,B	2643262	24-08-90
		IT-B-	1240765	17-12-93
		JP-A-	2255623	16-10-90
		JP-B-	6011703	16-02-94
WO-A-8901772	09-03-89	US-A-	4839342	13-06-89
		AT-T-	109970	15-09-94
		AU-B-	2421388	31-03-89
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		DE-T-	3851152	26-01-95
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		GR-B-	1000558	26-08-92
		JP-B-	6067850	31-08-94
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		CA-A-	1335566	16-05-95

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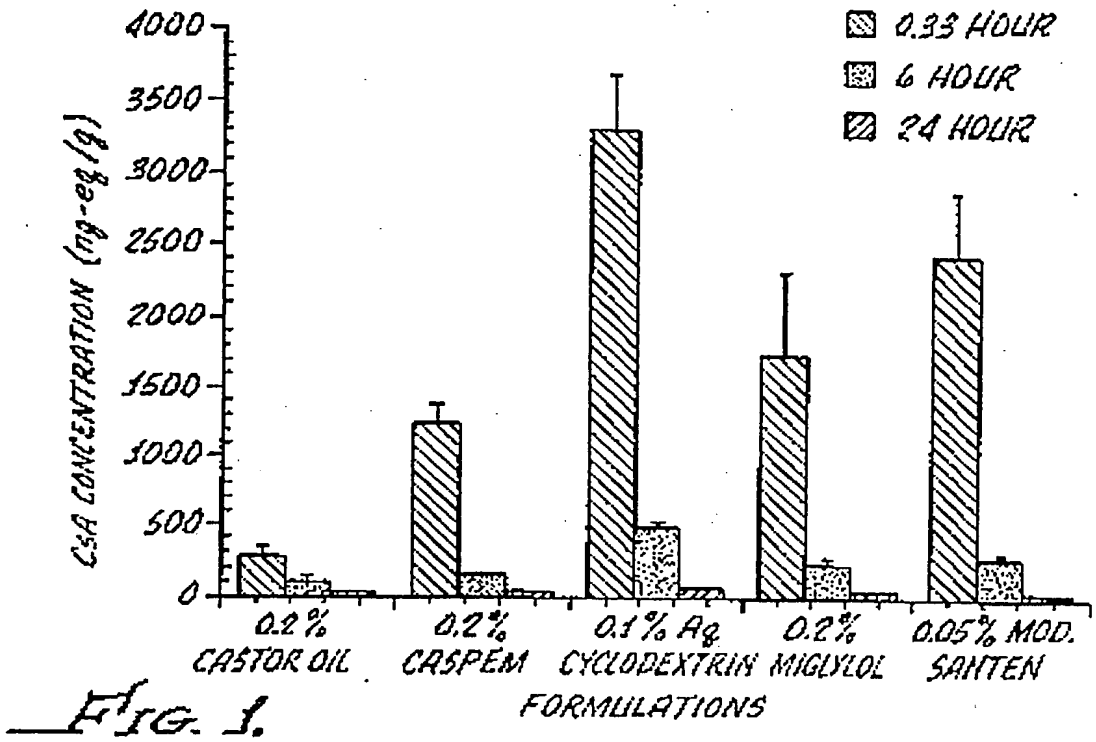

FIG. 1.

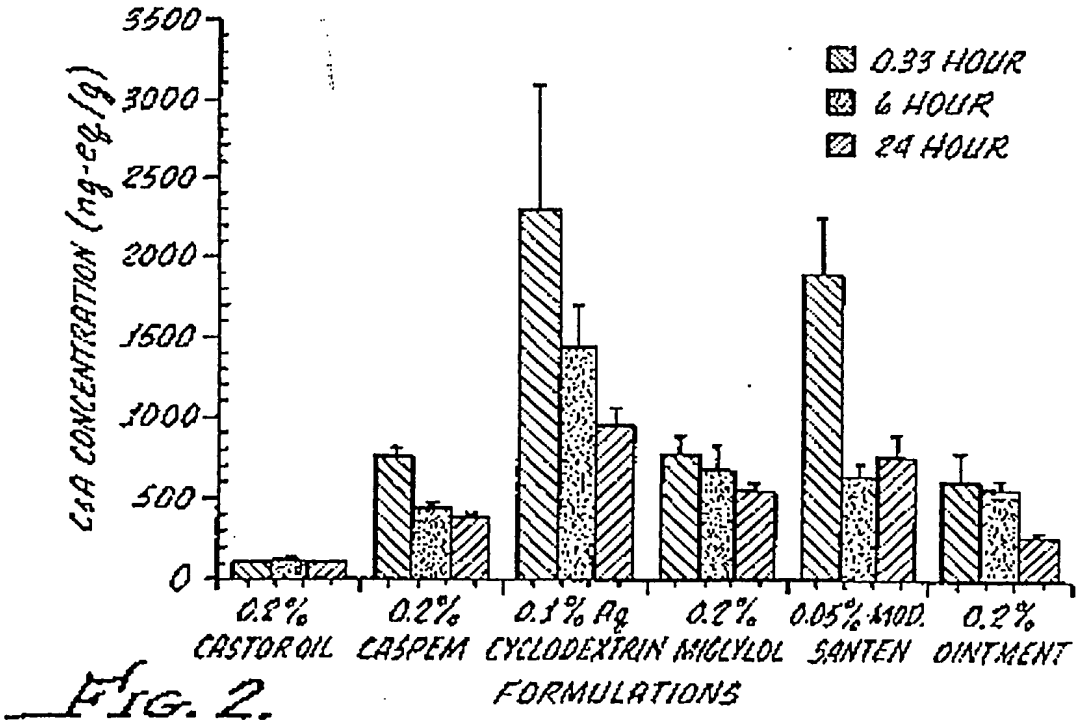

FIG. 2.

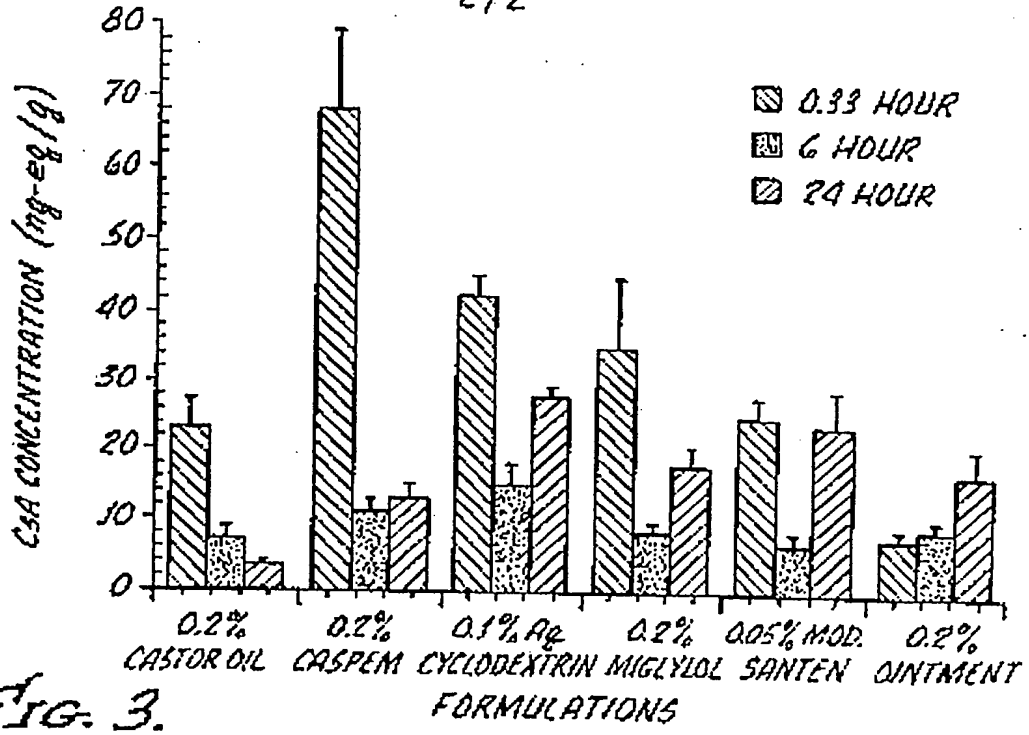
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FIG. 3.

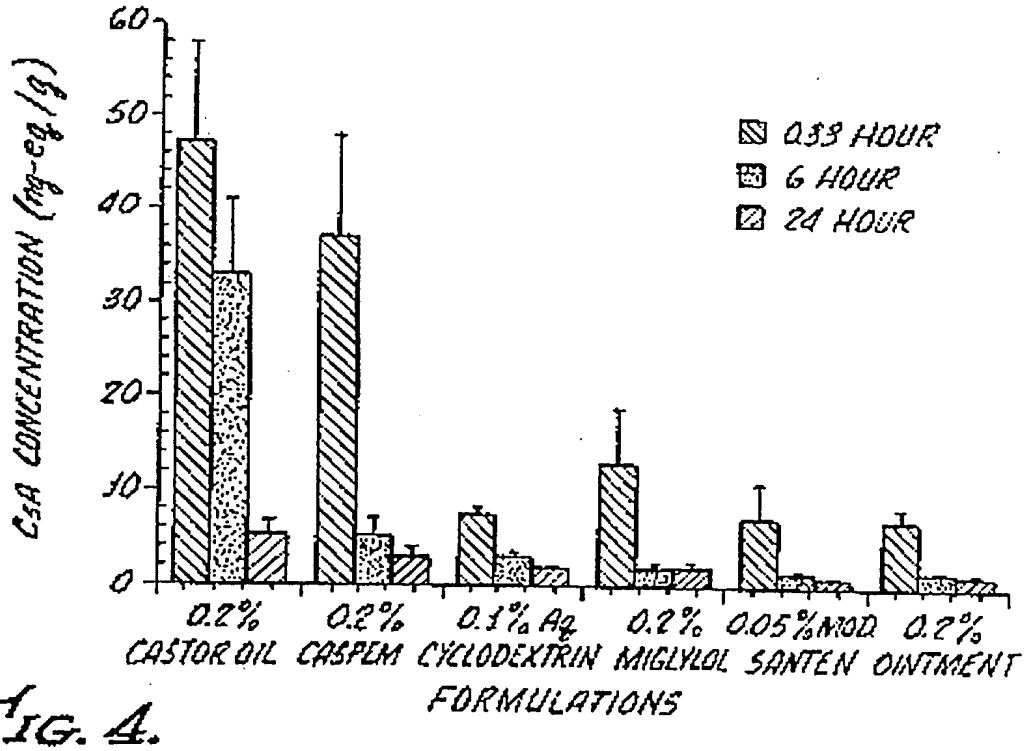
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FIG. 4.